European Journal of Pharmaceutical Sciences 111 (2018) 142–152

Contents lists available at ScienceDirect

European Journal of Pharmaceutical Sciences

journal homepage: www.elsevier.com/locate/ejps

Investigation of novel supersaturating drug delivery systems of chlorthalidone: The use of polymer-surfactant complex as an effective carrier in solid dispersions

Maria Terezinha França, Rafael Pereira Nicolay, Manoela Klüppel Riekes, Juliana Munari Oliveira Pinto, Hellen Karine Stulzer*

Programa de Pós-Graduação em Farmácia, Universidade Federal de Santa Catarina, Campus Trindade, 88040-970 Florianópolis, SC, Brazil

ARTICLE INFO

Keywords:
Chlorthalidone
Solid dispersions
Supersaturation
Spray drying
Soluplus-sodium lauryl sulfate complex
Biorelevant medium

ABSTRACT

Supersaturating drug delivery systems (SDDS), as solid dispersions (SDs), stand out among strategies to enhance bioavailability of poorly soluble drugs. After oral administration, their dissolution in gastrointestinal fluids often leads to supersaturation, which drives to a rapid and sustained absorption. Polymers and surfactants play important roles in SDs through inhibiting precipitation caused by transitions from amorphous into crystalline form, in supersaturated solutions, and also through improving SDs physical stability. Novel chlorthalidone SDs, a BCS IV drug, were developed using polymeric and non-polymeric carriers, specially a polymer-surfactant complex. SDs drug releases were evaluated using sink and non-sink conditions in water and biorelevant medium. Their physical stability was also monitored under different storage conditions. Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (SOL), sodium lauryl sulfate (SLS) and a combination of both showed promising results in apparent solubility studies, and therefore they were selected to compose the spray dried SDs. Dissolution studies demonstrated the SOL-SLS complex potential for providing chlorthalidone fast release (> 80% in 15 min), producing and maintaining *in vitro* supersaturation. This formulation comprising high drug loading (75%) reached a high supersaturation degree under non-sink condition (up to 6-fold the equilibrium solubility) once maintained for 6 h in biorelevant medium. In addition, this SD presented better physical stability when compared to the chlorthalidone neat amorphous. The SOL-SLS complex impacts positively on chlorthalidone release and physical stability, highlighting its potential as carrier in SDDS of a poorly soluble drug.

1. Introduction

Over the last three decades, the use of high-throughput screening methodologies has produced a growing number of drug candidates with poor aqueous solubility (> 80%), and consequently poor oral bioavailability (Williams et al., 2016). Development of formulation strategies to overcome this limited bioavailability has become one of the most important challenges for the pharmaceutical industry (Ghadi and Dand, 2017a; Stegemann et al., 2007). Many formulations approaches, to improve poorly soluble drugs dissolution and solubilization, have been developed. However, there has been rising realization that simply increasing the dissolution rate or solubilizing the drug is often insufficient to achieve the desired bioavailability. Consequently, the interest in delivery systems that lead to supersaturation has burgeoned (Taylor and Zhang, 2016).

Supersaturating drug delivery systems (SDDS) contain the drug in high energy form that provide drugs at concentrations above their equilibrium solubility into the intestinal milieu (Brouwers et al., 2009; Fong et al., 2016). The potential impact of this supersaturation on the transport of drugs across biological membranes has been documented through *in vitro* experiments, using both artificial and biological membranes. The flux across the membrane increases linearly along with a growth in free drug concentration and it continues to increase as the solution becomes progressively more supersaturated (Beig et al., 2017;

Abbreviations: BCS, Biopharmaceutics Classification System; CTD, Chlorthalidone; CMC, Critical Micelle Concentration; DE, Dissolution Efficiency; FTIR, Fourier Transform Infrared; HPLC, High Performance Liquid Chromatography; P188, Kolliphor P188®; PS2, Kolliphor PS20®; PM, Physical mixture; SOL, Polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer; RH, Relative Humidity; SLS, Sodium Lauryl Sulfate; SEM, Scanning Electron Microscopy; SDs, Solid dispersions; SDDS, Supersaturating Drug Delivery Systems; UV, Ultraviolet; XRPD, X-ray Powder Diffraction

* Corresponding author.
E-mail address: hellen.stulzer@ufsc.br (H.K. Stulzer).

http://dx.doi.org/10.1016/j.ejps.2017.09.043
Received 15 June 2017; Received in revised form 31 August 2017; Accepted 26 September 2017
Available online 28 September 2017
0928-0987/

Miller et al., 2012; Sun et al., 2016). In order to benefit from the supersaturated state, this condition has to be maintained for enough time until absorption happens. Once supersaturation is a metastable state and has the tendency to precipitate, this may require the use of pharmaceutical excipients that interfere in nucleation and/or crystal growth. A large pool of excipients has been explored as precipitation inhibitors; including polymers, surfactants and cyclodextrins (Brouwers et al., 2009; Fotaki et al., 2014; Warren et al., 2010). In this context, solid dispersions (SDs) are usually employed, and they typically contain the drug molecularly mixed with or physically suspended an inert carrier matrix (*e.g.* hydrophilic polymers, surfactants, *etc.*) (Sun et al., 2016; Vasconcelos et al., 2007). When SDs formulations are administered, mainly amorphous, dissolution in the gastrointestinal fluids often leads to supersaturation, which results in rapid and sustained absorption (Taylor and Zhang, 2016).

SDs are often evaluated using slightly adapted one compartment compendial dissolution methods. These compendial tests are usually run under sink conditions (large dissolution volumes or high surfactant concentration), and the literature pointed out that they are only suitable to kinetics test release, *e.g.* in a quality control context (Bevernage et al., 2013). Nowadays, several studies have been reporting the evaluation of SDDS under non-sink conditions, for poorly soluble drugs, in order to better correlate the *in vitro* dissolution with the *in vivo* precipitation behavior of the SDs in gastrointestinal fluids (Chen et al., 2015; Knopp et al., 2016; Krupa et al., 2016; Mah et al., 2016). Although, its known that an appropriate supersaturation evaluation is therefore the key for efficient development and optimization of SDDS, few studies have provided comparative studies of both sink and non-sink dissolution tests for the same supersaturating formulation (Bevernage et al., 2013; Sun et al., 2016).

Chlorthalidone (CTD, Fig. 1), a model drug used is this study, is a diuretic and antihypertensive drug, widely used over 50 years. It is considered as one of the first-choice compounds suitable for the antihypertensive treatment initiation and maintenance, either as monotherapy or in some combinations (Mancia et al., 2013). CTD is practically insoluble in water (190 μg mL^{-1} at 25 °C), has a pKa 9.4, a molecular weight 338 g mol^{-1} and a log P of 0.8 (Bonfilio et al., 2014; Moffat et al., 2011; United States Pharmacopeia, 2007). The literature reported four CTD polymorphs, among which the form I is the clinically preferred solid state for drug product manufacturing (Kountourellis et al., 1992; Kumar et al., 2005; Martins et al., 2009, 2012) CTD is commercially available as tablets from 12.5 to 100 mg (Joint Formulary Committee, 2016; Moffat et al., 2011). It is qualified as a BCS class IV drug (Wu and Benet, 2005), showing low solubility and permeability, and consequently leading to a limited bioavailability, around 65% (Moffat et al., 2011). A recent study reports that BCS class IV drugs, such as CTD, are still challenging regarding the bioavailability and achievement of an optimum therapeutic potential (Ghadi and Dand, 2017b).

Few studies have been reported in the literature involving approaches to improve CTD solubility and drug dissolution, among these are cited CTD SDs using carriers such as urea (Bloch et al., 1982), camphor, menthol, mannitol and polyvinylpyrrolidone K-12 (Raghavendra Rao et al., 2009). A SD involving a combination of CTD and polyvinylpyrrolidone resulted on a patent claimed by company Boehringer Ingelheim (Pandit and Horhota, 1984) and a pharmaceutical formulation marketed in the United States under the name of Thalitone®. However, none of these studies have explored the generation and maintenance of supersaturation for SDs of this drug.

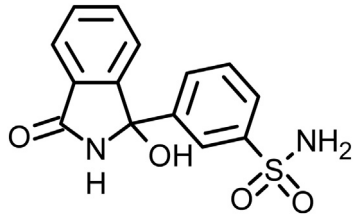

Fig. 1. Chemical structure of Chlorthalidone (United States Pharmacopeia, 2007).

The aim of this study was to develop and evaluate novel SDs of CTD as absorption-enabling strategy to increase the drug dissolution, under sink and non-sink conditions. The effect of carriers, especially a polymer-surfactant complex, was explored and investigated on the ability to produce and maintain the *in vitro* supersaturation state in aqueous and biorelevant medium. The physical stability and sink conditions release of SDs were also investigated, aiming to monitor their behavior during storage under defined conditions.

2. Materials and methods

2.1. Materials

CTD was obtained from Pharmanostra® (Rio de Janeiro, Brazil). Soluplus®, polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer (SOL), Kolliphor PS20®, polysorbate 20 (PS20), and Kolliphor P188®, poloxamer 188 (P188), were kindly provided by BASF® (São Paulo, Brazil). Sodium lauryl sulfate (SLS) was purchased from Dinâmica Química Contemporânea Ltda® (São Paulo, Brazil). The commercial product Higroton® 50 mg tablets was obtained from a drugstore. The ultrapure water was obtained from a Milli-Q system (Millipore, Bedford, USA). The biorelevant dissolution medium used was Fasted State Simulated Intestinal Fluid (FaSSIF) powder purchased from Biorelevant.com (Surrey, UK). All other chemicals used throughout the experiments were analytical or High Performance Liquid Chromatography (HPLC) grade.

2.2. Effect of carrier on apparent solubility of CTD

The solubility of crystalline CTD and the effect of the surfactants on the apparent solubility of this drug were evaluated in triplicate using a Varian model VK 7000 dissolution tester (USA). All the surfactants (P188, SOL, PS20 and SLS) were tested in two concentrations (1% and 2% w/v), both above their critical micelle concentration (CMC). An excess amount of drug was added to 275 mL of monobasic sodium phosphate buffer (pH 6.8) at a constant temperature of 37.0 ± 0.2 °C and 150 rpm for 24 h. Samples were filtered through a 0.45 μm polyamide membrane (Chromaphil® Xtra) and quantified by previously validated methodologies.

The samples quantification was carried out by ultraviolet (UV) spectroscopy, using a Cary 50 Bio UV–Visible spectrophotometer at λ = 275 nm for all samples, except those containing SOL. These samples were quantified by HPLC methodology, adapted from Youssef and coworkers (2013), using Shimadzu LC − 10 equipped with UV detector set at 275 nm, 20 μL of injection volume, under 25 °C. The stationary phase comprised a reversed-phase C18 analytical column (Purospher® STAR: 5 μm, 250 × 4.6 mm). The mobile phase consisted of methanol and sodium phosphate dibasic buffer solution pH 4.0 (isocratic mode, 45:55, v/v), at a flow rate of 1.0 mL min^{-1}. Both methodologies, UV and HPLC, were previously validated, presenting linear responses over the concentration range of 10–150 μg mL^{-1} and 2–75 μg mL^{-1}, respectively.

The two most efficient solubilizers (SOL and SLS) were investigated as a binary mixture of carriers, in order to verify their impact on the drug apparent solubility.

2.3. Preparation of CTD spray dried SDs

The amorphous CTD and SDs were prepared by spray drying. For the SDs, different amounts of surfactants, similar to those selected in Section 2.2, were dissolved in 600 mL of ultrapure water (solution 1). An amount of CTD (2.5 g) was solubilized in 150 mL of ethanol, at 60 °C